November-December 1960 Vol. 10 No. 6
Published by the American Cancer Society, Inc.

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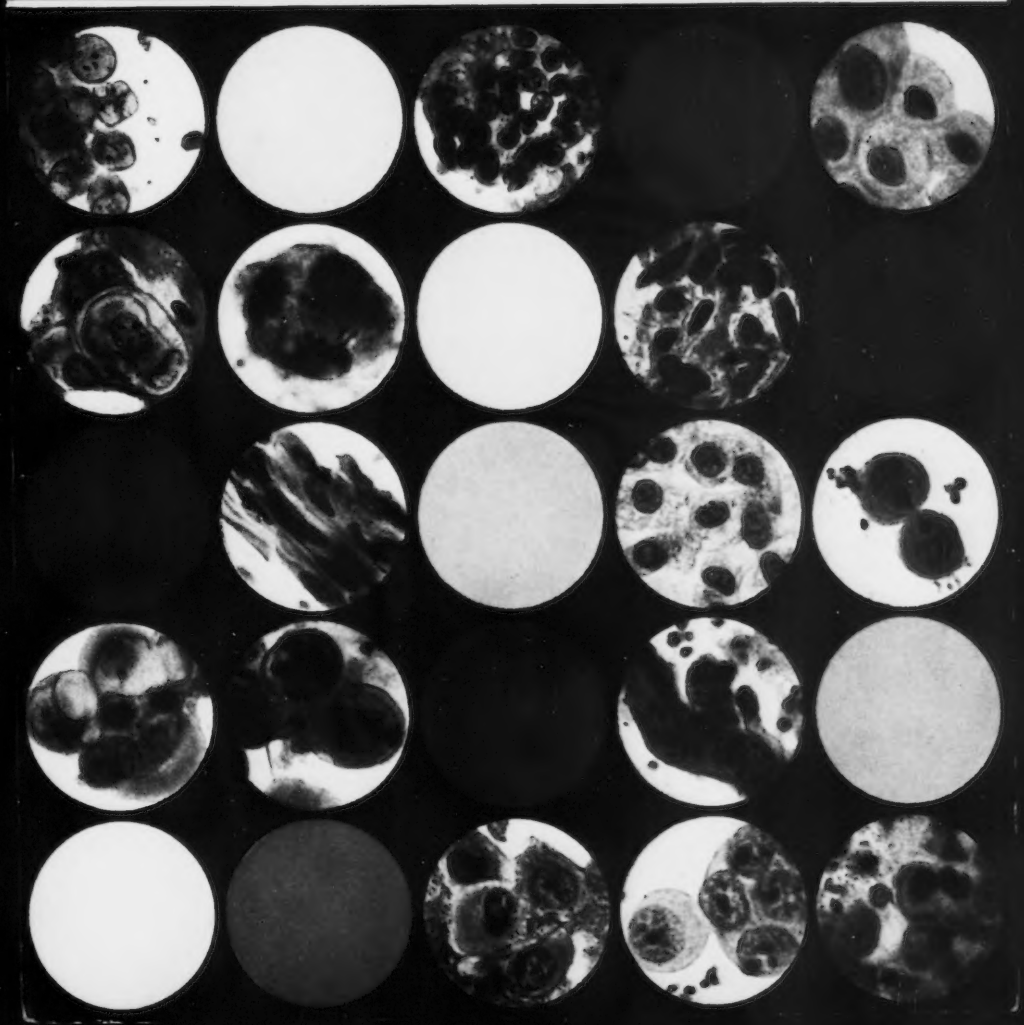
Bulletin of

Cancer Progress



certain questions still remain...

The opportunities for early diagnosis of cancer offered by the Papanicolaou test have brought with them certain problems. These are particularly well illustrated in the field of gynecology where cytologic techniques of diagnosis have had their greatest application.

The first problem concerns how much dependence may be placed on a negative cytologic report in the presence of some symptom that raises the possibility, however remote, that malignancy is present. Examples of such situations are those in which a woman in her thirties reports a single episode of intermenstrual bleeding or an older woman notes a trace of blood some years after the menopause. The question then is whether a negative Papanicolaou test diminishes at all the number of diagnostic curettages that must be carried out.

The answer, it seems to me, is that there are indeed situations in which the symptoms are the slightest and the physical findings essentially negative and where a negative Papanicolaou test will permit at least a delay in the undertaking of more extensive diagnostic procedures. In a woman after the menopause, this negative report should also have been obtained from endometrial biopsy. That phase of the use of cytology, where a technique is asked to exclude a suspected malignancy, is, however, one which needs much more study and in the meantime must be handled with the greatest caution.

The other set of problems concerns the application of screening techniques for the detection of cancer of the uterus in women without symptoms. Here the future course seems much clearer, but certain questions still remain: How often must examinations be repeated? What type of worker (physician, nurse or technical assistant) should carry out the mammoth undertaking, if the objective is to apply the test universally? How should women be persuaded to come for the tests? And last but not least: Who should pay for the tests—the patient or, perhaps, the state through its department of health? All of these questions must be answered, for with this test the practical elimination of death from cancer of the cervix is almost in our hands.

Howard C. Taylor

Cover—

Design by Don Smith, New York City.
Photomicrographs from the collection of Dr. G. N. Papanicolaou.

NEWSLETTER

NOVEMBER-DECEMBER, 1960

Notes from the FOURTH NATIONAL CANCER CONFERENCE which was held in Minneapolis on September 13-15, 1960:

Dr. Walter L. Mersheimer (New York Medical College), reporting the key findings of a vast study of cancer survival rates, revealed that five-year survival rates are increasing for all major types of malignancy except breast cancer. The nationwide survey, which included 212,368 patients, was carried out with the cooperation of 99 hospitals, a number of cancer registries and the National Cancer Institute. A significant increase in five-year survival rates in both sexes was found for cancer of the large bowel, rectum and thyroid. In women, notable improvement was observed for malignancy of the tongue, salivary glands, uterine cervix and corpus, Hodgkin's disease and melanoma of the skin.

There appears to be a clear-cut difference between men and women in respect to survival rates after surgery for localized lung cancer; in women, the five-year survival rate was 62%, as compared to only 30% in men. There was no apparent sex difference, however, among lung cancer patients who were treated nonsurgically or whose cancers had spread beyond the original site. The explanation for the difference is not known, but such factors as size, location, and histologic type of tumor, as well as the patient's endocrine status, are important elements which need further evaluation.

Dr. Sidney J. Cutler (National Cancer Institute), commenting on the five-year survival rate as the most widely used summary index for describing end results in cancer, stated that the observed increases in the five-year survival rates were in large part due to marked increases in the one-year survival rates, which in turn appear to have resulted from an increased use of surgery and a reduction in operative mortality. In general, changes in therapeutic policy and techniques reduced not only the initial, acute mortality risk, but also reduced the risk which persists for some years beyond the first year.

Dr. Gordon McNeer (Memorial Center, New York) reported that there is an appreciable number of patients complaining of ulcer symptoms who are treated medically for ulcer and then die later from cancer. He stated that gastric ulceration should be considered to be cancer (i.e., a surgical lesion) until proved otherwise. That this decision is justified became apparent when it was found that 30% of 234 patients who were operated upon for small gastric ulcerations were shown to have carcinomatous ulcers. The five-year survival rate in this group was high -- almost 39% -- as compared to the overall survival rate for stomach cancer -- 7%.

Dr. McNeer and his colleagues consider it imperative to remove surgically all small gastric lesions and identify them histologically. Almost all ulcerative lesions of the stomach which are over 2 cm in diameter should be excised at the earliest possible time.

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Dr. Philip J. Hodes (Jefferson Medical College, Philadelphia) described a radiologic procedure for detecting with high accuracy early, even unsuspected, breast cancer. The technique, developed by Dr. Robert L. Egan (M. D. Anderson Hospital, Houston), yields soft-tissue X rays which permit far more accurate differentiation between benign and malignant lesions than do conventional roentgenograms. Lesions as small as 8 mm in diameter have been identified. The technique utilizes fine-grain, type M industrial X-ray film and relatively low-energy beams in the range of 26 to 28 kv.

Such roentgenograms have been obtained on 4,000 women who were referred because of mammary or axillary symptoms. Follow-up of the first 1,000 who were X-rayed between 1956 and 1959 revealed 245 confirmed breast cancers, only two of which were "missed" by soft-tissue roentgenograms because they were not included in the X-ray field. Nineteen of the cancers spotted by this technique were not clinically apparent and had been unsuspected. Since the low intensity of the X-ray beam poses only minimal radiation hazard, the procedure may be highly useful in screening for breast cancer.

(Continued after page 212)

CA Bulletin of Cancer Progress

Published bimonthly by
AMERICAN CANCER SOCIETY, INC.
New York, N. Y.

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Address all correspondence to
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American Cancer Society, Inc.
521 West 57th St., New York 19, N. Y.

Annual Subscription $2.50

Special bulk rate to organizations other than Divisions subscribing in quantities of 200 or more.

Exfoliative Cytology of the Uterine Cervix and Vagina

Leopold G. Koss, M.D.

The great interest in exfoliative cytology at the present time is due chiefly to the ease, efficiency and accuracy with which it can be utilized for the detection of early cancer of the uterine cervix. With the help of a qualified cytopathologist, the practicing physician has within his reach a method of early diagnosis which can lead to the successful treatment of one of the most serious and frequently fatal diseases of the female genital tract. While most invasive cancers of the cervix may be readily recognized on clinical examination, the early stages of the disease and especially carcinoma in situ do not necessarily produce appreciable changes in the appearance of the cervix. In fact, the diagnosis of early cervix cancer may be established with certainty only by microscopic examination of tissues or cells derived from the lesion.

Diagnostic Principles

Biologic Principles

All epithelia of the body, whether normal or cancerous, continuously shed cells from their surfaces. Thus, cells desquamating from the uterine and vaginal epithelia may be readily obtained for microscopic examination from the vaginal cul-de-sac. In order to insure better diagnostic accuracy, *vaginal smears must be supplemented by smears obtained directly from the epithelial surface of the cervix.* The recognition of cancer cells within smears of exfoliated material prepared for microscopic examination constitutes the basis of cytologic diagnosis.

From the Memorial Hospital for Cancer and Allied Diseases, New York, N. Y.

This work was performed with the assistance of Mrs. Grace R. Durfee, B. S., Chief Cytotechnologist, Memorial Hospital for Cancer and Allied Diseases.

Technical Principles

The correct recognition of cancer is easier and more reliable if the cells are well preserved. Since drying will damage and distort the cells, it is important to obtain the best and most rapid fixation of the specimen. For this reason, *the bottle containing the fixative should be opened before the smears are taken* so that the smeared slides can be fixed immediately. The writer recommends the following fixatives for genital smears, in order of preference: (1) equal portions of 95% ethyl alcohol and ether; (2) 95% ethyl alcohol; (3) isopropyl alcohol (absolute).

Papanicolaou staining[13] is much preferred to any other staining method because it assures cytoplasmic transparency and cellular differentiation superior to any obtainable by other methods.

Methods of Obtaining Smears

The best possible accuracy in cytologic diagnosis is achieved if both a vaginal and a cervical smear are submitted to the laboratory. The smears should be evenly spread and placed immediately in the fixative. Obtaining smears at the time of menses should be avoided. The patient should not douche for 24 hours before the smears are taken.

VAGINAL SMEARS — The vaginal smear should be obtained as the very first procedure in the gynecologic examination.

Lubricants should be avoided because they interfere with staining and obscure cellular detail. The vaginal smear can be effectively used for the determination of various changes within the epithelium of the genital tract, but *it fails in the detection of in situ carcinoma of the cervix in about 30 per cent to 40 per cent of cases. However, the vaginal smear is indispensable in the detection of endometrial carcinoma.*

CERVICAL SMEARS — Cervical smears should be obtained under direct vision. All lubricants must be avoided when introducing the speculum. If there is difficulty in inserting the speculum, particularly in postmenopausal women with an extremely atrophic and dry vaginal mucosa, the instrument should be moistened with *normal saline solution.*

There are two methods of obtaining cervical smears: the cotton-tipped applicator may be used, or the wooden scraper, as first suggested by Ayre, which is readily prepared by cutting a tongue depressor to the required shape. Both methods are extremely efficient in disclosing the presence of cervix cancer, whether in situ or invasive. The cotton swab, if not too thick, may be introduced farther into the canal, a fact occasionally of some importance. The wooden scraper is potentially somewhat traumatic, but the smears are richer in cells. The use of either method is largely a matter of personal preference.

The cervical smear is generally ineffective in the detection of endometrial cancer.

ENDOCERVICAL ASPIRATION — Considerable information may be obtained by aspirating the endocervical canal by means of a small cannula attached to a syringe. The method is used routinely in some centers. It is very efficient in detecting endocervical cancer but may fail if the lesion is located on the portio or in the vagina. Endometrial cancer may be diagnosed quite often in this manner.

SELF-OBTAINED SMEARS — Several devices, such as the tampon,[2] have been designed which can be introduced into the vagina by the patient herself. The tampon can later be withdrawn by the patient or a nurse and then smeared on slides. The advantage of self-obtained smears lies in the fact that a large number of screening procedures can be performed on many women under the supervision of a small medical staff. The disadvantages of this method are its relatively low sensitivity and the difficulty encountered in the interpretation of material. The latter is due to the cellular distortion resulting from smearing the tampon. The method also deprives the patient of an opportunity for a complete pelvic examination. Finally, the introduction and the withdrawal of the tampon may cause discomfort for postmenopausal women with atrophic vaginas. Self-obtained smears are recommended only if the more conventional methods of obtaining cytologic material cannot be applied. However, if the choice is limited to this smear or no smear at all, the self-obtained smear may prove to be of a distinct advantage.

INFORMATION FOR LABORATORY

As with any laboratory procedure, it is unwise to let the cytopathologist look at the specimen without having necessary information about the patient. In order to protect both the clinician and the pathologist and to assure the patient of maximum diagnostic reliability, the following information should be provided with every specimen: (1) age; (2) menstrual history and date of last menstrual period; (3) clinical findings and diagnosis, and (4) past history of treatment, particularly cautery, surgery, radiation, chemotherapy, etc., even if not applied to the genital tract.

Scope and Value of Cytology

Considerable skill is required for the correct interpretation of cytologic specimens. Mere fluency in histologic diagnosis is not sufficient criterion of diagnostic ability in the field of exfoliative cytology, but it constitutes an excellent background for further training and experience. Knowledge of normal cytology is an essential prerequisite for attempting to make the diagnosis of cancer. Besides serving as a tool for cancer diagnosis, the smears may provide a variety of types of useful information. These will be mentioned briefly for completeness and clarity.

Normal Cytology

The vagina and the vaginal portion of the cervix (the portio) are lined by stratified squamous epithelium which normally does not become keratinized (Fig. 1). The superficial squamous cells which desquamate from such an epithelium during the child-bearing age have abundant cytoplasm and small nuclei (Fig. 2). Occasionally cells from the deeper epithelial layers may be present in smears. Such cells have less cytoplasm, are generally smaller and, depending on the layer of origin, are classified as intermediate, parabasal or basal. At certain times, such as prior to sexual maturity, during the first weeks postpartum, or after the menopause, the maturation of the squamous epithelium may not go beyond the stage of parabasal cells (Fig. 5).

The endocervical canal is lined with a layer of tall, mucin-producing columnar cells. The numerous endocervical glands are lined in a similar manner (Fig. 3). The characteristic columnar appearance of endocervical cells is evident in cervical smears (Figs. 2 and 4). Endocervical cells are uncommonly seen in vaginal smears. The point of transition between the endocervical glandular cells and the squamous epithelium of the portio is referred to as the squamocolumnar junction. The junction is usually located in the general vicinity of the external os.

Benign Cervix Lesions

INFLAMMATION — *Trichomonas vaginalis*, a parasite which is a very common cause of vaginitis and cervicitis, may be readily identified in cervical and vaginal smears (Fig. 6). *Candida albicans (Monilia)* may also be readily recognized. The cytologic changes caused by severe inflammatory processes, especially those due to trichomonads, may present some difficulties in interpretation.[9] Cellular atypias due to inflammation may, in rare instances, be suspected of being carcinoma; conversely, cancer cells may be mistaken for inflammatory cells or remain concealed within the debris and inflammatory exudate in smears.

Occasionally it is a wise course to clear up the infection by *conservative measures* and then repeat the cytologic examination. Drastic therapeutic measures, such as electrocautery, applications of silver nitrate, etc., should be avoided as they may only contribute to the confusion of the cytologic picture.

EROSION — The so-called cervical erosion is a sharply demarcated area of redness which appears on the surface of the portio adjacent to the external os. The lesion is often caused by the presence of transparent endocervical mucosa replacing stratified squamous epithelium on the surface of the cervix. The vessels in the underlying stroma are visible through the thin mucosal layer and account for the red appearance of the area. The term *eversion* or *ectropion* of the endocervical mucosa is more descriptive and should be applied to this entity. A cytologic smear is quite effective for differentiating a superficially ulcerating carcinoma from eversion. The eversion sheds only benign columnar cells of the endocervical type, often arranged in papillary clusters.

LEUKOPLAKIA — Areas of excessive and abnormal keratin formation on the surface of the squamous epithelium of the cervix appear clinically as white patches and have therefore been called leukoplakia (Fig. 7). Leukoplakia may be due to a variety of mechanical factors, such as prolapse, pessary, etc. It may also be present on an area of cervix previously treated by cauterization. Leukoplakia results in the presence of keratinized anuclear "squames" in smears (Fig. 8). The relatively uncommon keratinizing cervix cancers may appear clinically as foci of leukoplakia. Such cancers shed abnormal cells and may be differentiated cytologically from the benign lesions.

Effects of Treatment on Smears

CAUTERY — Cauterization of the cervix may cause a marked distortion of cells to the point of their being confused with cancer. Since these effects may persist for as long as six weeks, the pathologist should always be informed that the procedure was previously carried out.

RADIATION — Radiation may cause an immediate and a late effect. The immediate effect of radiation is manifested by cellular and nuclear enlargement, vacuolization, multinucleation and nuclear abnormalities. The late effect of radiation may persist for a great many years; the writer has observed one case in which it was apparent 19 years after completion of radiation treatment. Considerable cellular and nuclear distortion which are occasionally present may be misinterpreted as cancer, unless one is aware of the possibility of such changes.

ANTIBIOTICS — Certain broad-spectrum antibiotics when applied topically may produce massive desquamation of the epithelium and thus *conceal the presence of cancer*. No antibiotics should be used topically for at least *one month* before smears are taken.

Carcinoma of the Cervix

CLASSIFICATION — Although two different types of epithelium occur within the cervix, most cervix cancers originating on the portio or in the endocervical canal are of the squamous or epidermoid type. Adenocarcinoma of the cervix is relatively uncommon but may occasionally be found side by side with epidermoid cancer. In some instances, mixed or muco-epidermoid forms of cancer may occur which contain elements of both epidermoid and mucus-producing cancer.

IN SITU CARCINOMA — Considerable evidence is now available that invasive carcinoma of the cervix is preceded by in situ carcinoma. In situ carcinoma is best defined as a form of cancer still confined to the epithelium.

In situ epidermoid carcinoma is characterized histologically by a profound upheaval in the structure of the squamous epithelium (Fig. 9). There is a loss of orderly stratification and maturation. The component cells vary in size and display marked nuclear abnormalities. Mitotic figures, normal or abnormal, may be readily observed. An extension of the process into the endocervical glands is not infrequent and does not constitute evidence of invasion.

During the last 50 years, evidence has accumulated that in situ carcinoma of the cervix can progress to invasive cervix cancer. Stoddard, in 1952, found 42 such cases in the literature. Numerous additional cases have been observed since that time. In a vast prospective study, Petersen followed (without major treatment) 126 patients with lesions of the cervix epithelium that correspond quite closely to in situ carcinoma and related abnormalities. Approximately one third of these patients developed invasive cervix cancer within nine years of observation. The period of evolution of in situ carcinoma to invasive carcinoma may be quite long; Galvin has reported a period of 16 years in one case. Statistical evidence demonstrates that patients with invasive cervix cancer are, on the average, five to 10 or more years older than patients with in situ carcinoma.[19]

It is important to note that in some instances in situ carcinomas of the cervix cannot again be demonstrated after the initial biopsy or after very superficial treatment. This was found in approximately 25 per cent of cases of in situ cancer and related lesions (which had no significant treatment) followed in our institution for several years.[9] It is felt that this course of the disease is secondary to the removal of the major portion of the lesion by biopsy forceps. It is likely that, in a favorable case, the regenerating healthy epithelium is able to dislodge some of the minute foci of cancer left behind. There are also numerous instances on record in which in situ carcinoma was found incidentally in uteri removed surgically for other reasons[5] and in autopsy material from women who died of unrelated causes. Thus, many women with in situ carcinoma may lose their uteri or their lives from other causes before developing invasive cervix cancer.

The total evidence accumulated to date suggests that invasive cervix cancer is preceded by in situ carcinoma in most, if not all, cases. On the other hand, not all in situ cancers will necessarily progress to invasion within the lifespan of the bearer.

Since it is not possible to prognosticate the outcome of in situ carcinoma on the

strength of the histologic examination," nor to ascertain the duration of an in situ carcinoma prior to detection, the lesion should be considered a potentially dangerous one. *Its very slow evolution, however, removes it automatically from the category of surgical emergencies.*

The prognosis of treated in situ carcinoma of the uterine cervix is excellent. No cases of metastases from in situ carcinoma have been reported, according to our knowledge. Very nearly 100 per cent of cases treated by one of the many approaches available survive five years or longer without evidence of disease. Only sporadically are cases reported in which a recurrence of the disease was noted.[11] We have observed a few such cases with a recurrence in the vagina after the initial treatment by hysterectomy.

Since the prognosis of invasive cervix cancer is not nearly so favorable, it is obvious that cervical cancer should be diagnosed and treated electively in the in situ stage. Undoubtedly, even the keenest methods of investigation will occasionally fail to detect early cervix cancer, and it may well be that in an exceptional case the course of the disease is so fulminating that there is no time for early detection. However, these situations are so uncommon that they should not detract from the value of a sustained search for early cervix cancer, preferably in the in situ stage.

It must be emphasized here that in situ carcinoma may be present as a "cancerous coating" at the periphery of invasive cancer. Because of differences in the therapeutic approach to the two forms of cervix cancer, it is essential that sufficient tissue evidence be obtained prior to therapy in order to insure that no invasion is present.

EPIDERMOID CANCER — The cytologic diagnosis of epidermoid cancer is based on recognizable cellular changes in smears. These changes pertain chiefly to the nuclei and, to a lesser degree, to the cytoplasm of cancer cells.

The nuclear changes readily noted are: enlargement; abnormally dark staining or hyperchromasia, due to an increase in some nucleoproteins (desoxyribonucleic acid); irregularities of size, shape and chromatin pattern; presence of abnormal nucleoli; and abnormally high mitotic or premitotic activity. As a result of nuclear enlargement without a corresponding increase in the surrounding cytoplasm, the surface ratio of the nucleus to the cytoplasm is changed in favor of the nucleus.

The cytoplasmic changes comprise: cytoplasmic irregularities, abnormal keratin formation and development of bizarre-shaped cells. There may also be a marked variation in cell size (Figs. 10 and 14).

DIFFERENTIAL DIAGNOSIS — It is often possible to make the diagnosis of in situ carcinoma on cytologic grounds.[17] In addition to cells of frank cancer as defined above, in situ epidermoid cancers shed cells which characteristically have a well differentiated and normally abundant cytoplasm surrounding an abnormal nucleus. Such cells were called *dyskaryotic* by Papanicolaou[14] and may be classified into superficial, intermediate, parabasal, and endocervical types, depending on their layer of origin as indicated by their cytoplasmic features (Fig. 12). The presence of these cells indicates that a certain tendency toward epithelial maturation may be expected to exist within the cervix lesion, a property that is usually reserved for in situ carcinoma. While dyskaryotic cells also may be present in smears of invasive cancer, they will be few in number. These criteria, if judiciously used by experienced observers, may be quite helpful in ruling out invasion on cytologic grounds. They are not infallible, however. Histologic confirmation should be made before treatment is started.

TREATMENT OF IN SITU CANCER — Treatment of any neoplastic lesion depends on its prognosis. The lesion of known benign behavior requires merely local removal. Lesions known to metastasize are, as a rule, treated radically by surgery or radiation in the hope that they will be removed or destroyed as completely as possible before distant spread has occurred; invasive cervix cancer belongs to this category of lesions.

In situ carcinoma without invasion is a lesion quite comparable to Bowen's disease of the skin and, as a general rule, is

curable by simple surgical removal. There is, however, a considerable difference of opinion as to whether this removal should take place by means of local treatment of the cervix or by hysterectomy. While the writer does not feel qualified to settle this controversy, he would like to point out that he has had an opportunity to observe numerous cases of in situ carcinoma, previously treated by extensive conization or trachelectomy, that did not show any evidence of recurrence over periods ranging from three to five years.[9] Cytologic follow-up is mandatory after limited therapy.

On the other hand, there is evidence that this type of treatment may not be sufficient in some instances, because the lesion may be beyond the reach of the conization knife.[10] Several such cases have been observed by the writer. This observation would tend to support the view held by some physicians that a total hysterectomy with a wide vaginal cuff is the treatment of choice for extensive in situ cancer. Whichever mode of therapy is chosen, *in situ carcinoma is not a surgical emergency* and may be treated electively and without urgency.

IN SITU CARCINOMA AND PREGNANCY — Cumulative evidence at this time indicates that in situ carcinoma in the pregnant woman is essentially the same lesion as in situ carcinoma in the nonpregnant woman.[10] In keeping with our knowledge of the slow evolution and excellent prognosis of in situ carcinoma, it appears completely permissible to let the patient with this lesion complete her pregnancy. The writer has knowledge of several patients with untreated in situ carcinoma who went through pregnancy and vaginal delivery without any undue effects. It would seem, therefore, that even in these instances in situ cancer should be treated electively, at a time selected by the physician after consultation with his patient.

BORDERLINE LESIONS — Cytology is an extremely sensitive method for detecting abnormalities of cervix epithelium. A certain percentage of abnormal smears is due to the presence of epithelial lesions which by our present criteria cannot be classified as in situ cancer[7,18] (Figs. 11 and 12). These lesions have been classified by various authors as atypical hyperplasia, dysplasia, borderline atypias, koilocytotic or warty atypias, etc. Their behavior varies markedly and cannot be predicted on cytologic or histologic grounds. Some lesions may disappear without any known treatment or after a biopsy, but some of these lesions persist and are, in all likelihood, stages in the genesis of cervix cancer[12] and should be classified as precancerous. Such epithelial abnormalities may be found adjacent to in situ and even invasive cancer, and the possibility of this association should be kept in mind at all times. Also, invasive cervix cancer has been known to follow such lesions and *it would be erroneous to leave these lesions untreated unless the patient can be watched very carefully over a period of years for signs of developing carcinoma.*

The treatment should be guided by the degree of abnormality observed in histologic material. Conservative treatment, such as local removal of the borderline lesions by extensive cauterization or conization, appears to be quite adequate and preserves the reproductive function of patients in the child-bearing age.

It should be pointed out also that the nomenclature and classification of such lesions vary from laboratory to laboratory and depend largely upon the individual pathologist's approach to the problem. Such lesions may readily become "shopping lesions", and if they are examined by different authorities they will be given various labels ranging from "atypia" to "in situ carcinoma". The writer believes that the nomenclature of such early neoplastic lesions is immaterial, provided they are recognized and not dismissed as of little importance.

ADENOCARCINOMA — Mucus-producing adenocarcinomas shed vacuolated columnar cells with markedly abnormal nuclei. Papillary adenocarcinomas shed papillary clusters which often cannot be differentiated from other forms of adenocarcinoma originating anywhere within the genital tract, or from adenocarcinomas arising elsewhere and becoming metastatic to the genital tract (Figs. 15 and 16). The

muco-epidermoid variety of cervix cancer sheds primarily cells of the epidermoid type among which may be found vacuolated, mucus-containing cancer cells.

RECURRENT CERVIX CANCER — Cytology offers an excellent opportunity for the detection of recurrent carcinoma of the cervix, irrespective of whether surgery or radiation was used to treat the primary tumor. The cells of recurrent carcinoma are usually free of any radiation effect. It is of interest to note that carcinoma of the cervix recurring after treatment by radiation appears occasionally as in situ carcinoma.[8]

Confirmatory Biopsy

Any cytologic report suggesting or diagnosing cervix cancer of any type must be confirmed by biopsy before definitive therapy is instituted. The reasons for this procedure may be briefly summarized as follows:

1. Cytologic study, regardless of how accurately it is performed, gives only limited information about the location or extent of the lesion. It is of particular importance to realize that invasive cancer may be found where none was suspected on cytologic grounds.

2. While a lesion of the cervix may be observed clinically and the cytologic report may indicate the presence of cancer, the lesion may prove to be benign; the cancer cells may have originated from an area not noted on clinical examination.

3. The relatively short period of time that the cytologic techniques have been in use accounts for a certain margin of diagnostic error that may vary according to the examiner's experience. The role of inflammatory processes, radiation, cauterization, etc., as potential sources of cytologic error, have already been discussed.

It has to be realized that cytologic smears may reflect epithelial alterations which are geographically extremely small and measure only a few millimeters in diameter. Therefore, the epithelium should not be damaged prior to biopsy. *Any energetic scrubbing of the cervix almost invariably results in the removal of the epithelium and therefore may render the biopsy completely valueless.* Only the most gentle preparations should be applied to the cervix.

Multiple Biopsies

Multiple biopsy specimens should not be taken blindly and thrown together into a bottle. *Each specimen should be kept in a separate bottle, numbered and geographically designated* so that an opinion can be formed as to the extent of the lesion present. Also, *such biopsy specimens should always include the external os of the cervix* which is the area of greatest concentration of in situ cancer.[4] One way of obtaining geographically designated specimens is the so-called four-point biopsy method: one specimen is taken from a point in each of the four quadrants of the cervix—for example, at 12, 3, 6 and 9 o'clock.[4]

Schiller's iodine test is very helpful in discovering areas of epithelial abnormality, including in situ carcinoma.[21] Such areas are poor in glycogen and therefore do not stain with iodine.

The chief advantage of cervix biopsies is that they can be performed as an office procedure and do not require hospitalization. A disadvantage is the relatively limited amount of information that small tissue fragments can give, especially as regards the existence of invasive carcinoma.

Cold Knife Conization

This procedure consists of removing a conical portion of cervix in such a way that the base of the cone surrounds the external os and the apex is within the endocervical canal. The cone should always be marked by means of a suture at a predesignated area, such as, at 12 o'clock. *All of the tissue obtained by conization must be examined histologically;* otherwise, grave omissions and diagnostic errors may occur.

Conization by means of electrocautery is definitely not advisable because it injures the integrity of the tissues which must be examined microscopically.

Conization offers a very good sampling of material from the cervix. If a large cone

fails to disclose invasive cervix cancer, the chances are negligible that such a lesion exists within the cervix. The procedure may also be curative in some cervix lesions. The chief disadvantages of conization are the necessity of hospitalization, however brief, and the fact that it may produce considerable bleeding.

Curettage

If the previously described methods of diagnostic confirmation of cervix lesions fail, an endocervical or endometrial curettage may occasionally disclose the existence of the lesion.

Failure of Confirmation

In a certain percentage of cases, usually not exceeding 0.5 per cent of all suspicious or positive smears, efforts at confirmation of the existence of a cervix lesion may fail. Under these circumstances, it is advisable to initiate a search for a vaginal lesion (see below), an endometrial or ovarian lesion, or a metastatic lesion. If this search is consistently negative and the smears have become negative after extensive biopsies, recutting and examining the biopsy material previously obtained may reveal the existence of a minute focus of in situ carcinoma which was not present in the initial sections of tissue.

Diagnosis of Vaginal Cancer

Primary malignant tumors of the vagina fall essentially into two groups: the botryoid sarcoma, a variety of rhabdomyosarcoma occurring chiefly in the vaginas of children, and the carcinomas affecting women usually after 40 years of age. Cytology has no place in the diagnosis of botryoid sarcoma, but it may be very successfully applied to the detection of carcinoma of the vagina.

Carcinomas of the vagina are usually of the epidermoid or squamous type. Very little is known at the present time about the duration of the in situ stage since the lesion is comparatively rare. However, even very small, locally invasive cancers of the vagina may produce distant metastases and therefore the behavior of this tumor differs substantially from that of cervix cancer.

Carcinomas of the vulva may also occasionally be the source of abnormal cells.

Cytology

Cytologic presentation of vaginal or vulval squamous carcinoma is indistinguishable from that of cervical carcinoma.[3] The main difference is the distribution of cells within the smears: cells of cervix cancer will be abundant in the cervical smear and scanty in the vaginal smear, while cells of vaginal cancer will be scanty in the cervical smear and abundant in the vaginal smear. Therefore, if no lesion can be found in the cervix, despite the presence of cells of epidermoid or squamous carcinoma, it is imperative to investigate the vagina.

It should be kept in mind that vaginal lesions may occasionally be hidden behind the cervix. In such circumstances, examination under anesthesia, utilizing the Schiller test for guidance, or obtaining smears (appropriately labeled) from various areas of the vaginal mucosa may prove to be distinctly advantageous.

Early carcinoma of the vagina may be quite inconspicuous, appearing clinically as a red or white patch. Biopsies of such areas may reveal the source of abnormal cells.

In view of the serious prognosis of vaginal carcinoma, immediate and appropriate therapy should be instituted when such a lesion is discovered. Under no circumstances, however, should therapy be applied before the lesion is localized and then evaluated by biopsy.

Metastatic Tumors

Metastases from distant sites or extension of cancer from adjacent organs may also be observed in the genital tract of the female. The writer has noted cancer cells in genital smears in several cases of mammary carcinoma as well as in other metastatic tumors having their primary origin elsewhere. It is important to emphasize that primary cervical or vaginal carcinoma may occur in the presence of cancer elsewhere in the body.

Summary

Our present general knowledge pertaining to the early stages of cancers of the cervix and the vagina may be summarized as follows:

1. By application of cytology to the detection of cervix cancer in the in situ stage, it is within the reach of the medical profession to reduce very significantly the mortality rate due to this disease.

2. All, or nearly all, of the carcinomas of the cervix are preceded by the stage of carcinoma in situ.

3. In situ carcinoma may remain stationary for periods varying from one to 10 years or longer. If adequately treated, the prognosis is excellent.

4. The evidence presently available suggests that not all in situ cancers invariably develop into invasive cervix carcinoma within the lifespan of the patient.

5. The presence of in situ carcinoma in limited biopsy material calls for further investigation of the cervix to rule out the concomitant presence of invasive cervix cancer.

6. If invasion has been ruled out, in situ carcinoma ceases to be a surgical emergency. It can be treated electively and without urgency.

7. In the presence of cytologic findings which suggest epidermoid or squamous carcinoma, a thorough search should be instituted for carcinoma of the vagina or the vulva, if the lesion cannot be localized within the cervix.

8. Metastatic cancers from sites other than the genital tract may occasionally be the cause of positive genital smears.

Legends

Fig. 1. Normal squamous epithelium of cervix and vagina. (× 233)

Fig. 2. Mature squamous cells as seen in cervical and vaginal smears. In the center there is also a cluster of ciliated endocervical cells. (× 935)

Fig. 3. Normal endocervical mucosa. Note tall mucus-secreting cells. (× 233)

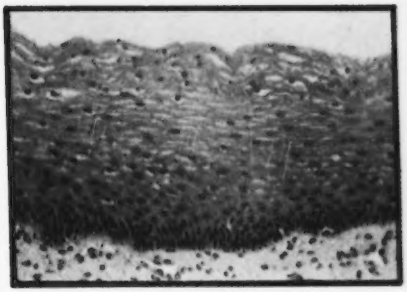
Fig. 4. Normal endocervical cells in smears. (× 935)

Fig. 5. Appearance of a smear in advanced postmenopausal atrophy. Note small size of squamous cells and numerous inflammatory cells in the background. (× 935)

Fig. 6. *Trichomonas* infestation in vaginal smear. The parasite is an oval, greenish gray body with a small peripheral nucleus. Squamous cells show a moderate nuclear atypia. (× 935)

Fig. 7. Hyperkeratosis of cervix with epithelium presenting clinically as a white patch or leukoplakia. (× 233)

Fig. 8. Anuclear squamous cells originating from the surface of leukoplakic mucosa. (× 935)



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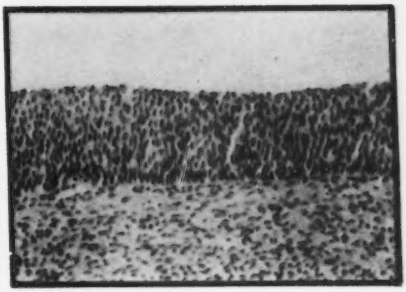

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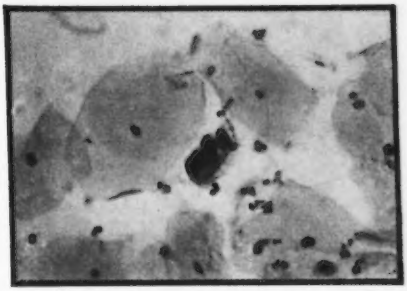

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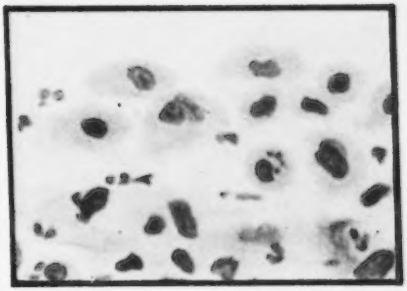

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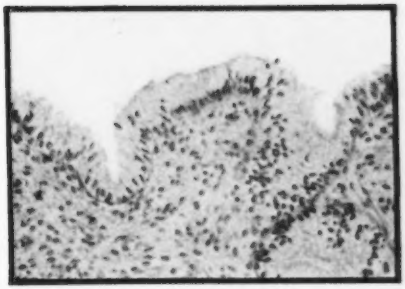

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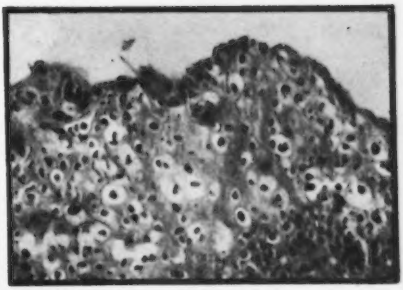

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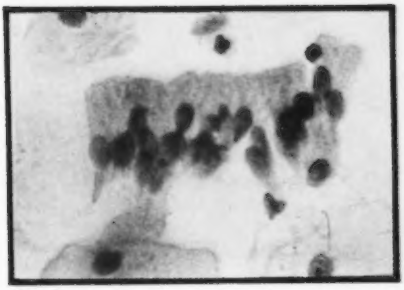

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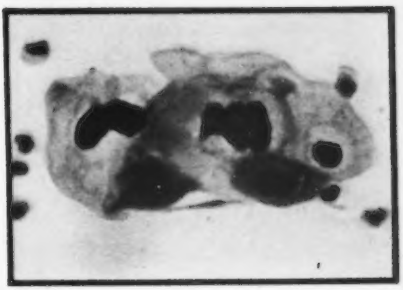

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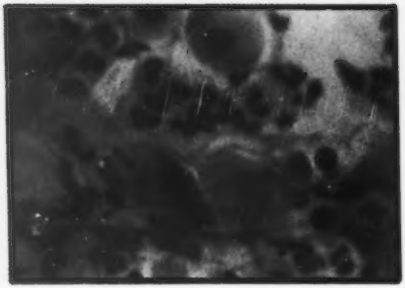

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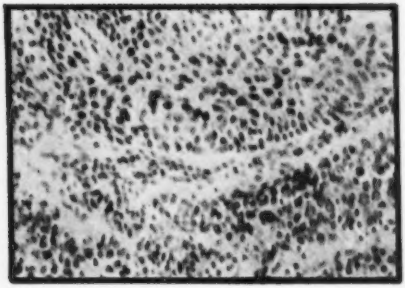

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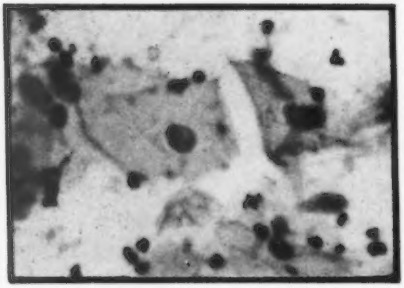

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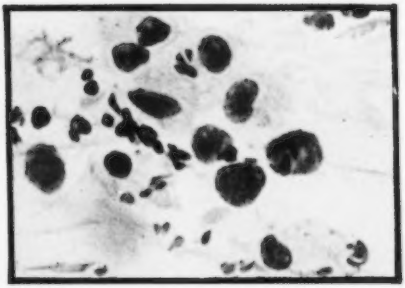

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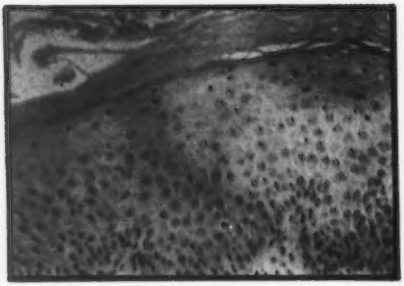

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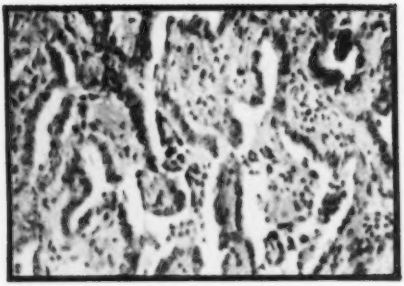

Fig. 14.

Fig. 15.

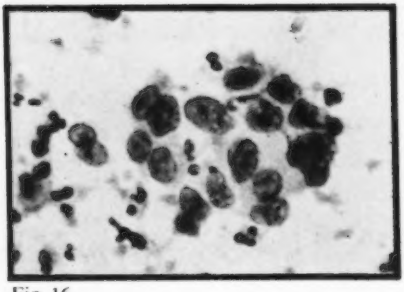

Fig. 16.

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Legends

Fig. 9. Epidermoid carcinoma in situ of the cervix. Note abnormal make-up of the epithelium as compared with Fig. 1. (× 233)

Fig. 10. Appearance of a cervical smear from the same case as Fig. 9. Note marked nuclear abnormalities. (× 935)

Fig. 11. Borderline atypia of cervix epithelium. Observe nuclear abnormalities and good epithelial stratification. Lesion does not warrant the diagnosis of in situ carcinoma but may precede it, or may be associated with it. (× 233)

Fig. 12. Dyskaryotic squamous cells from the same case as shown in Fig. 11. Note cytoplasmic differentiation and nuclear abnormalities. (× 935)

Fig. 13. Invasive epidermoid carcinoma of cervix. (× 233)

Fig. 14. Cells from the same case as Fig. 13. Note nuclear abnormalities and nearly total absence of any cytoplasmic differentiation. (× 935)

Fig. 15. Adenocarcinoma of the endocervix. (× 233)

Fig. 16. Cells from same case as Fig. 15. Note nuclear abnormalities and especially prominent nucleoli. (× 935)

Endometrial Cytology

Hanns-Werner Boschann, M.D.

Papanicolaou and Traut reported in 1943 that carcinoma of the corpus uteri (adenocarcinoma of the endometrium) can be detected by means of cytological examination of the vaginal and cervical secretions. A number of investigators have since confirmed this statement. However, most of these authors found that diagnostic accuracy is greater for squamous carcinoma of the cervix than for adenocarcinoma of the endometrium. The main reasons for this discrepancy are the following: (1) it is more difficult to differentiate between benign and malignant cells in the endometrium than in the cervix; (2) in order to obtain well preserved cells from the uterine cavity, it is often necessary to resort to intrauterine aspiration.

Vaginal and Endocervical Smears

Vaginal and endocervical smears yield a relatively low degree of diagnostic accuracy which may be attributed mainly to two factors: (1) as the endometrial cells pass from the uterine cavity into the vagina, they undergo degenerative changes and (2) if there is stenosis or complete block of the internal os, tumor cells may be entirely absent from the vaginal smears, even in the case of advanced carcinoma of the endometrium. Furthermore, even a positive reading does not always tell the reader whether he is dealing with carcinoma of the endocervix or adenocarcinoma of the endometrium. Nevertheless, occasionally even latent carcinoma of the endometrium has been detected by vaginal smears and some authors report a cytodiagnostic accuracy of 80 per cent or more with this technique.[11,13,23,28,29]

From the Free University of Berlin and Rudolf Virchow Hospital, West Berlin, Germany.

Intrauterine Aspiration

The method of intrauterine aspiration yields a diagnostic accuracy of about 84 per cent[30] and represents the most efficient procedure for cytological diagnosis of adenocarcinoma of the endometrium. In 96 cases of endometrial carcinoma which we studied, the number of positive cytological findings obtained was as follows:

a. Smears from the posterior fornix	31	(32%)
b. Endocervical smears	59	(61%)
c. Intrauterine aspirations	83	(86%)

Various techniques have been devised for obtaining material from the uterine cavity. Cary employs a rigid metal cannula, 28 cm long; Hecht,[14] a thin, flexible laryngeal cannula with beveled end, an instrument which has not caused a single perforation of the uterus in 4,350 aspirations; Clyman, a cannula with four openings and mandrin; Rubin et al., a modified insufflation cannula; Winer et al., a soft polyethylene tube; Ayre, a rotating endometrial brush consisting of a polyethylene tube with retractable bristles; Nieburgs, an endometrial cannula with retractable nylon fibers; and Boschann,[3] a nylon brush within a metal tube (Figs. 1 and 2). The last three techniques are designed to eliminate contamination of the specimen with endocervical cells. Navratil advises the use of a pessary in order to enrich the smear with endometrial cells, a procedure which is also recommended by Bajardi but rejected by Israel et al. We use a flexible laryngeal cannula according to the techniques devised by Kleegman and by Speiser, if the endocervical canal is sufficiently wide and the anatomical conditions clear

Kleegman's technique is as follows. The patient is put on the examining table in the lithotomy position and the vaginal fornices, ecto- and endocervix are cleansed and disinfected. If necessary, the anterior lip of the cervix is grasped with a tenaculum. A sterile antrum cannula, connected to a sterile 10 cc syringe, is then introduced into the uterine cavity for a distance of about 1.25 cm from the fundus uteri. After the first aspiration, the syringe is detached, closed and reattached and the aspiration repeated a second and third time, the cannula being slightly withdrawn each time. The contents of the cannula are expelled onto a glass slide and evenly distributed. The slide is then immediately placed into a mixture of 95% alcohol and ether; the aspirated tissue particles are carefully removed and also fixed in alcohol-ether for subsequent histological examination.

Speiser recommends the use of a Killian cannula, shaped in accordance with the flexion and version of the uterus. The cannula is connected to a 10 cc Boston-Record syringe and then introduced into the uterine cavity. Aspiration is begun as soon as the slightest resistance is felt. During aspiration the cannula is gradually retracted and moved back and forth within the uterine cavity by means of manipulation of the syringe, a procedure which allows collection of material from the entire uterine surface. If the cervical canal is narrow or the form and position of the uterus not clearly definable, small polyethylene tubing is used instead of a cannula. Its introduction can be achieved with a sterile forceps without causing any difficulty or discomfort, even when the internal os is narrow, as in the case of a senile patient or a nullipara. Aspiration is then carried out until material appears in the transparent tubing. The specimen is subsequently expelled onto glass slides in three portions, the second of which usually contains uncontaminated intrauterine material.

If the aspiration is unproductive, the uterine cavity can be lavaged with 2 cc of a sterile, normal saline solution which is introduced through the tubing and immediately aspirated. This aspirate is then mixed with an equivalent amount of alcohol-ether for immediate fixation of at least 20 minutes. This mixture is centrifuged at 2,500 rpm for 15 minutes and the sediment spread on an albumin-coated glass slide for subsequent staining according to the Papanicolaou technique. The sediment may, however, be embedded in paraffin, sectioned and stained. If there is considerable contamination with red blood cells, the smears should be placed in 10% acetic acid for five minutes,[16] or in alcohol-ether containing 6% acetic acid for 60 minutes.[6] This treatment will hemolyze the red blood cells, yet will have no effect on the staining properties of the endometrial cells. Staining is then carried out according to the Papanicolaou technique.

Only examiners with sufficient knowledge of the normal and pathological endometria should make the cytological diagnosis.

Normal Endometrium

Smears from the normal endometrium vary according to age, phase of the menstrual cycle and ovarian function of the individual patient (Figs. 3, 4, 5).[25] For all benign conditions the cellular material is characteristically uniform, i. e., the nuclei are round or oval, equal in size and have similar chromatin structure; the chromatin is arranged in small granules and the nuclear membranes appear distinct and smooth.[1,28]

Malignant Endometrial Cells

The malignant endometrial cell is characteristically irregular,[15,24,28] although this irregularity is less easily recognizable in the highly differentiated cells. Malignant cells contain nuclei which usually (1) have an irregular membrane and are unequal in size (anisokaryosis), and (2) show increased chromatin in irregular arrangement (hyperchromasia) (Fig. 6). In differentiated forms the cells are often found typically arranged back to back (Fig. 7). Rosette-like patterns indicate papillary growth (Fig. 8).

Undifferentiated cells which have no clear cytoplasmic details reveal their glan-

dular origin by the characteristic group formation, overlapping of the nuclei, eccentric positioning of the nuclei and vacuolization of the cytoplasm (Figs. 9 and 10). When adenoacanthoma is present, metaplastic as well as adenocarcinomatous cells are found which are similar to cells originating from squamous carcinoma.[12, 19, 28] In the case of sarcoma of the endometrium, stromal cells with characteristic nuclear polymorphism will be seen in the smears (Fig. 14).[10] In the case of endometrial polyps (Fig. 11) and glandular hyperplasia (Fig. 12), the cells show only slight anisokaryosis and the chromatin pattern is finer and more regular than in malignant cells. Postmenopausal smears[7] are likely to display cells containing small and regular nuclei, a finding (in senile bleeding) that facilitates cytodiagnostic differentiation between glandular hyperplasia and carcinoma (Fig. 13). In doubtful cases cytometric evaluation of the nuclei is most reliable.[9]

Summary

Endometrial smears that have been properly obtained and fixed permit an accuracy of not less than 80 per cent in the cytological diagnosis of carcinoma or sarcoma of the endometrium. The general practitioner should therefore use the cytologic method routinely (1) when there is suspicion of the presence of a tumor in the uterine cavity, particularly where it is impossible or inadvisable to perform curettage, or (2) when curettage does not yield sufficient material for histological examination. In the latter case, smears can be made directly from the curetted material and fixed immediately.

No examination for the detection of cancer is complete without cytologic study of the endometrium. Patients revealing suspicious smears should be recalled for repeat studies. If the reading remains doubtful or is indicative of the presence of malignancy, uterine curettage should be performed. The method of endometrial cytology should not replace curettage but can be used to determine which cases should be studied histologically. On the other hand, its use may help to reduce the number of unnecessary curettages.

Legends

Fig. 1. Endometrial brush within its tube, placed in uterine cavity.

Fig. 2. Endometrial brush in contact with endometrium, the tube having been withdrawn a distance of 4 to 8 cm, depending upon the size of the uterus.

Fig. 3. Endometrial glandular cells from a 29-year-old patient, ninth day of menstrual cycle. Brush material. (× 1250)

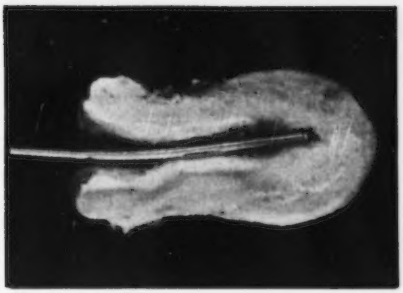
Fig. 4. Endometrial glandular cells, same patient, 18th day of same menstrual cycle. Brush material. (× 1250)

Fig. 5. Normal endometrial cells. Upper left: proliferation phase, ninth day. Lower left: glandular hyperplasia. Upper right: secretion phase, 18th day. Lower right: decidual cells in endometritis (post abortum). Brush material. (× 1250)

Fig. 6. Endometrial carcinoma showing anisokaryosis and hyperchromasia. Aspiration smear. (× 1250)

Fig. 7. Endometrial carcinoma showing back-to-back arrangement of cells. Aspiration smear. (× 500)

Fig. 8. Endometrial carcinoma showing rosette-like arrangement of cells indicating papillary growth. Aspiration smear. (× 800)



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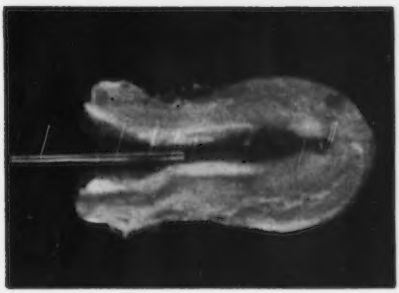

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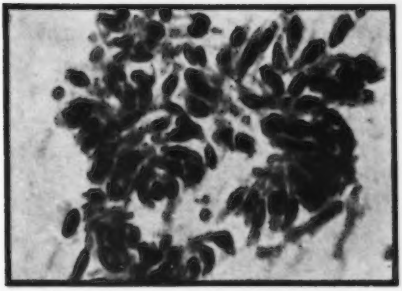
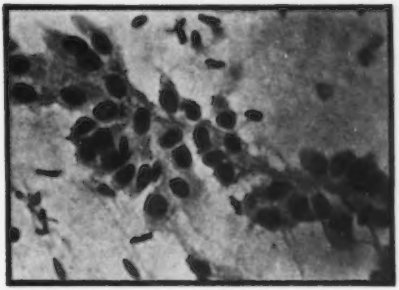


Fig. 3.



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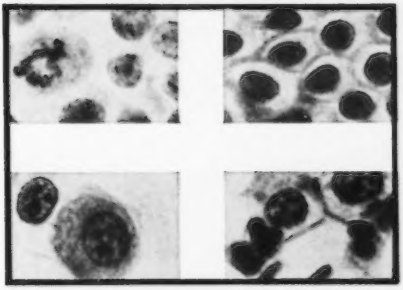
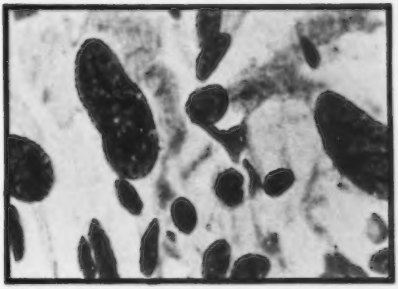


Fig. 5



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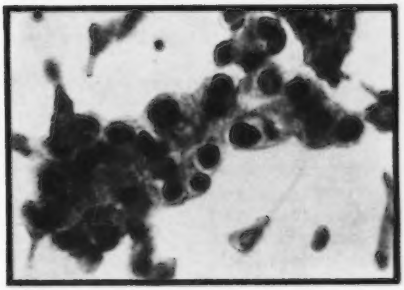

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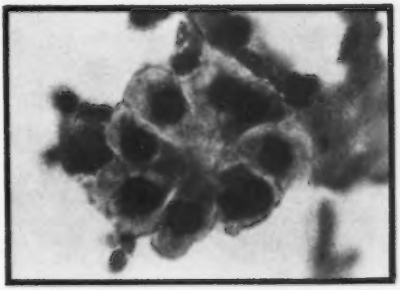

Fig. 8.

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Legends

Fig. 9. Endometrial carcinoma showing group of cells with degenerating cytoplasm. Endocervical smear. (× 1250)

Fig. 10. Smear showing histiocytes with foamy cytoplasm, vacuoles and bean-shaped nuclei with fine granular chromatin. Brush material. (× 1250)

Fig. 11. Endometrial polyp cells showing slight variation in size and shape but having "benign" chromatin structure. Brush material. (× 1250)

Fig. 12. Cells from glandular hyperplasia showing variation in size and shape, slight hyperchromasia but regular distribution of chromatin. Brush material. (× 1250)

Fig. 13. Postmenopausal smear showing cells with small, regular nuclei. Brush material. (× 1250)

Fig. 14. Sarcoma cells showing nuclear polymorphism. Aspiration smear. (× 500)

Fig. 15. Chorionic multinucleated giant cell. (Same elements can be seen in chorioepithelioma). Endometritis post abortum. Aspiration smear. (× 1250)

Fig. 16. Langhans' giant cell. Endometritis tuberculosa. Aspiration smear. (× 1250)

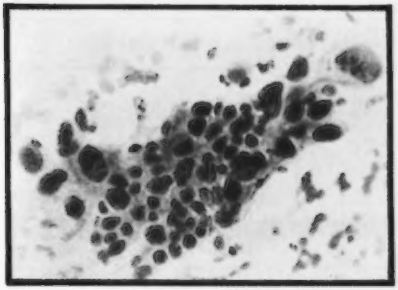
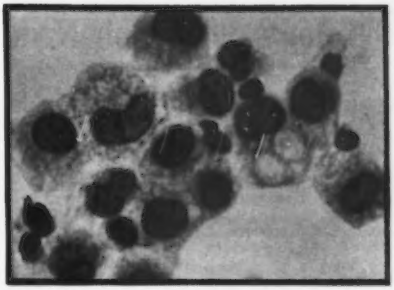


Fig. 9.



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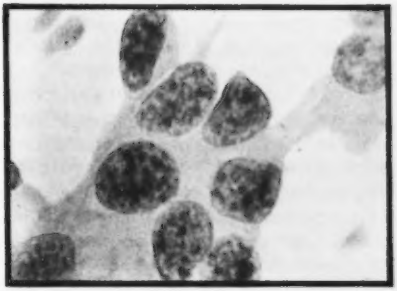

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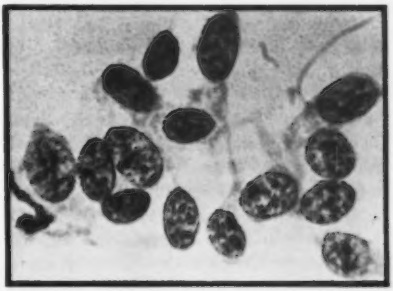


Fig. 12.

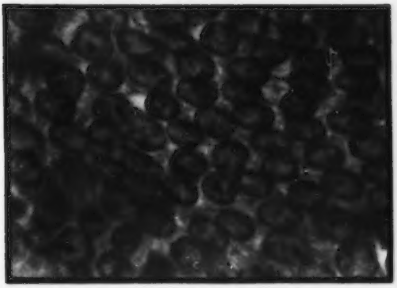
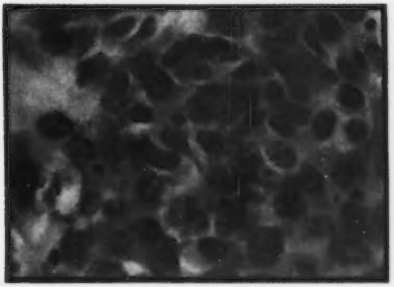


Fig. 13.



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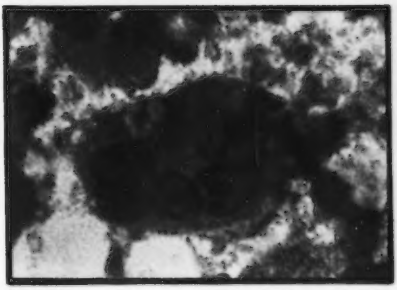

Fig. 15.

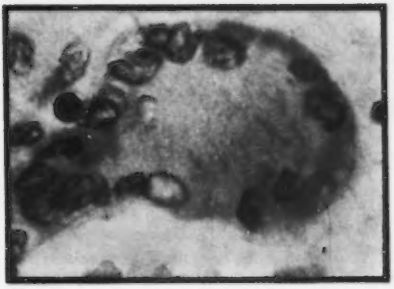

Fig. 16.

Cytology of Lymph Node Imprints

Irena Koprowska, M.D., John E. Ultmann, M.D.
and Ralph L. Engle, Jr., M.D.

The importance of determining the nature of persistent and unexplained palpable lymph nodes by early biopsy has been stressed by many investigators. As in other pathologic studies, the simultaneous use of sections and touch preparations of the excised material may be useful.

Enlargement of lymph nodes may result from benign disease or malignant growth. There are several types of lymphoma which vary in the rapidity of their course and which represent primary (i.e., intrinsic) neoplasms of lymph nodes. In males, lymphoid tissue is a leading primary site of cancer during adolescence.[1] Lymph nodes are frequently the site of metastatic tumors, mostly of the carcinoma type. According to Willis, 69 per cent of 426 consecutive cases of carcinoma autopsied in his laboratory had metastases in lymph nodes. Usually, metastases of carcinoma in lymph nodes offer no problem as the primary site is readily apparent. Cases do occur, however, where a palpable lymph node or skin involvement may be the first sign of disease, and a biopsy of the tissue may be the first histologic evidence of malignancy.[3]

Can malignant neoplasms of lymph nodes be diagnosed by cytologic methods? Would the addition of such methods to the routine diagnosis of cancer of lymph nodes be of value to the practicing physician? Smears and imprints of excised lymph nodes and smears from lymph node aspirates have been used for many years as an adjunct to, or in place of, routine sections. Papanicolaou's multiple polychrome stains (EA-36 and EA-65) or Wright-Giemsa stain were used according to the preference of investigators.[2,4,5] The following methods for preparing, fixing and staining lymph nodes were found satisfactory in our laboratories.

Freshly biopsied lymph nodes are bisected with a sharp scalpel. Half of the specimen is grasped by tooth forceps and the cut surface is touched lightly several times, without smearing, to clean slides. The slides are allowed to dry in air and then are stained by the Wright-Giemsa technique, or they are immediately fixed in ether-alcohol (equal amounts of 95% alcohol and ether) and stained by the Papanicolaou method, using EA-65. The half lymph node which is used for making imprints is then fixed in 10% formaldehyde and used for tissue studies. The remaining half may be used for bacteriological tests and fungus cultures.

For a proper evaluation of lymph node imprints by the cytologic technique, a brief description of various cell types encountered under normal and abnormal conditions appears to be profitable.

From the Hahnemann Medical College, Philadelphia, Pa. (Dr. Koprowska); Columbia University College of Physicians and Surgeons (Dr. Ultmann); and Cornell University Medical College (Dr. Engle), New York, N. Y.

Wright-Giemsa Stain	EA-65 Stain

Lymphocytes

(Figs. 1, 2, 3, 10, 11, 12, 19, 20)

Small lymphocytes are usually round and have scanty, pale blue cytoplasm. The nucleus is round or slightly indented and has a distinct nuclear membrane and very dark, moderately coarse chromatin. There are no nucleoli visible. *Medium* lymphocytes are slightly larger and usually round, although they may be oval or pear-shaped. The cytoplasm is more abundant but also stains light blue. The nucleus is round and the chromatin is less intensely stained and less clumped. No nucleoli are seen. *Large* lymphocytes differ from medium lymphocytes primarily in size.

The distinction between *small* and *medium* lymphocytes is often difficult. In both, the nuclei occupy almost the entire cell; there is a narrow rim of cytoplasm around the nucleus in medium lymphocytes. The nucleus stains dark blue or purple; the chromatin is coarsely granular with the heaviest granules distributed against the inner aspect of the nuclear membrane. *Large* lymphocytes differ from small and medium lymphocytes not only in their size, but also in their more finely granular chromatin network with large chromatin clumps and in their greater amount of cytoplasm.

Reticulum Cells

(Figs. 1, 2, 3)

These cells are frequently found in lymph node imprints. They are large, irregular, round or elongated and have poorly outlined cellular borders. The cytoplasm is finely granular and stains grayish blue. The clearly outlined nucleus is usually round and has stippled blue chromatin and a single blue-staining nucleolus.

Reticulum cells appear singly, in groups, or as syncytial aggregates. They are large, pale-staining cells with irregular outlines. Their nuclei, which are the same size as the nuclei of large lymphocytes, are oval, round or indented and have a finely granular chromatin network and a delicate membrane. The cytoplasm is abundant and usually stains pink.

Macrophages

(Figs. 7, 8, 9)

Macrophages resemble mature reticulum cells but contain a variable number of inclusions, such as azurophilic granules, vacuoles or debris. Numerous macrophages loaded with deep greenish brown granules of variable size are seen in hemosiderosis. Dark brown granules are seen in anthracosis.

Fixed tissue macrophages are distinguished from the reticulum cells only by the presence of cytoplasmic inclusions of phagocytized, often pigmented material. Hemosiderin stains reddish brown; anthracotic pigment stains black. Histiocytes (i.e., free macrophages), have an oval or round, rather than irregular, outline and finely vacuolated cytoplasm.

Wright-Giemsa Stain	EA-65 Stain

Polymorphonuclear Leukocytes

These cells are readily recognizable by either staining method because of their characteristic multilobular nucleus. They are seen in small numbers in chronic lymphadenitis and are more frequent in subacute lymphadenitis.

Eosinophilic Leukocytes

These cells are occasionally seen. They are recognized by their eosinophilic granules which are coarse and refractile.

These cells can be recognized by their coarse, granular cytoplasm which stains intensely red.

Plasma Cells

Plasma cells are the same size as medium lymphocytes. Their nuclei are eccentric. They have a coarse, intensely grayish blue cytoplasm and occasionally a clear perinuclear zone. The nuclear chromatin may be homogeneous or clumped.

These cells are oval and have eccentric, round nuclei. The distribution of chromatin resembles that seen in the nuclei of small and medium lymphocytes. The cytoplasm is more abundant than it is in lymphocytes. These cells are nearly always present in chronic lymphadenitis.

Legends

Fig. 1. Reticulum cell and lymphocytes. Chronic lymphadenitis. Imprint. (Wright-Giemsa. × 2600)
Fig. 2. Reticulum cell and lymphocytes. Chronic lymphadenitis. Imprint. (EA-65. × 2600)
Fig. 3. Reticulum cell and lymphocytes. Chronic lymphadenitis. Section. (H. & E. × 2600)
Fig. 4. Epithelioid cells. Imprint. (Wright-Giemsa. × 2600)
Fig. 5. Epithelioid cells. Imprint. (EA-65. × 2600)
Fig. 6. Epithelioid cells. Section. (H. & E. × 2600)
Fig. 7. Macrophage loaded with hemosiderin. Hemosiderosis. Imprint. (Wright-Giemsa. × 2600)
Fig. 8. Macrophage loaded with hemosiderin. Hemosiderosis. Imprint. (EA-65. × 2600)
Fig. 9. Macrophage loaded with hemosiderin. Hemosiderosis. Section. (H. & E. × 2600)
Fig. 10. Medium lymphocytes. Lymphocytic lymphosarcoma. Imprint. (Wright-Giemsa. × 2600)
Fig. 11. Medium lymphocytes. Lymphocytic lymphosarcoma. Imprint. (EA-65. × 2600)
Fig. 12. Medium lymphocytes. Lymphocytic lymphosarcoma. Section. (H. & E. × 2600)
Fig. 13. Lymphoblasts. Lymphoblastic lymphosarcoma. Imprint. (Wright-Giemsa. × 2600)
Fig. 14. Lymphoblasts. Lymphoblastic lymphosarcoma. Imprint. (EA-65. × 2600)
Fig. 15. Lymphoblasts. Lymphoblastic lymphosarcoma. Section. (H. & E. × 2600)
Fig. 16. Malignant reticulum cells. Reticulum cell sarcoma. Imprint. (Wright-Giemsa. × 2600)
Fig. 17. Malignant reticulum cells. Reticulum cell sarcoma. Imprint. (EA-65. × 2600)
Fig. 18. Malignant reticulum cells. Reticulum cell sarcoma. Section. (H. & E. × 2600)

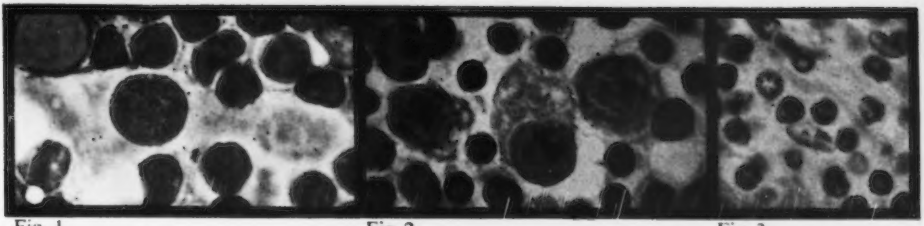

Fig. 1. Fig. 2. Fig. 3.

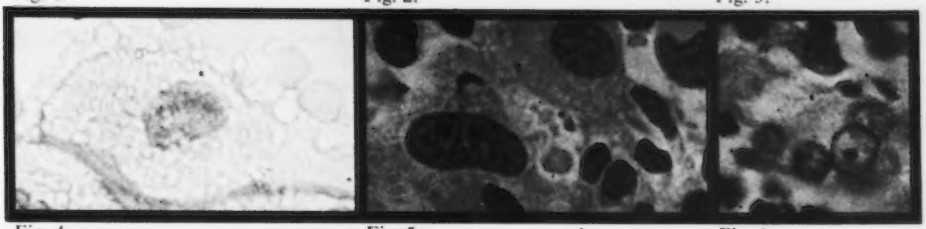

Fig. 4. Fig. 5 Fig. 6.

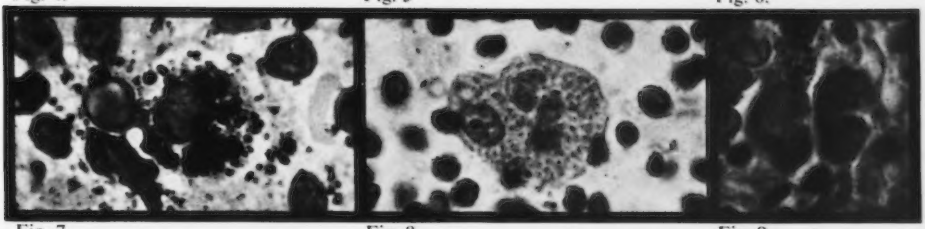

Fig. 7. Fig. 8. Fig. 9.

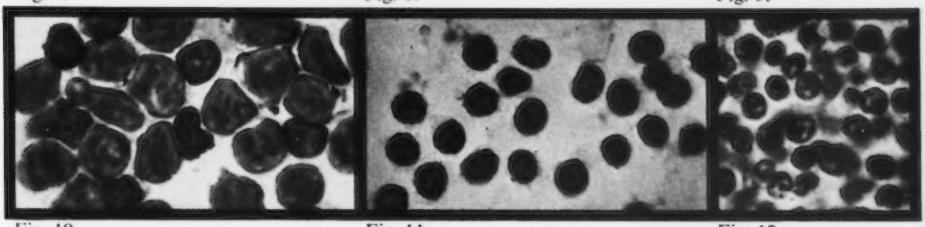

Fig. 10. Fig. 11. Fig. 12.

Fig. 13. Fig. 14. Fig. 15.

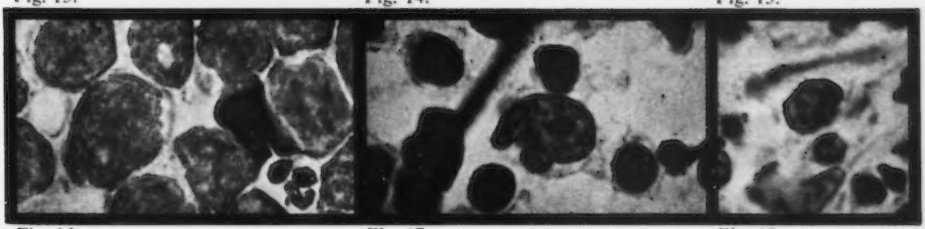

Fig. 16. Fig. 17. Fig. 18.

Wright-Giemsa Stain	EA-65 Stain

Mast Cells

Mast cells are the size of large lymphocytes. They are present in most smears but are especially noticeable in chronic lymphadenitis. The nucleus stains pale and is not conspicuous. The cytoplasm is entirely filled with prominent, uniform granules which stain bluish black.

These cells are the size of large lymphocytes or larger. They are oval-shaped and have a small, round, centrally placed nucleus. The chromatin is finely granular and stains deep blue or purple. There are no nucleoli. The cytoplasm is filled with purple granules, but these granules are much less conspicuous than they are in the Wright-Giemsa preparation.

Epithelioid Cells
(Figs. 4, 5, 6)

These cells resemble reticulum cells but may be much larger. They have abundant cytoplasm which is vacuolated and stains blue. The nucleus is relatively small and well outlined; it contains fine, stippled chromatin and one nucleolus. The cellular borders are distinct.

These cells differ from reticulum cells by having denser and more deeply pink-staining cytoplasm which may contain vacuoles.

Legends

Fig. 19. Immature lymphocytes and mitosis. Giant follicular lymphosarcoma. Imprint. (Wright-Giemsa. × 2600)

Fig. 20. Young lymphocytes. Giant follicular lymphosarcoma. Imprint. (EA-65. × 2600)

Fig. 21. Multinucleated Reed-Sternberg cell. Hodgkin's granuloma. Imprint. (Wright-Giemsa. × 2600)

Fig. 22. Multinucleated Reed-Sternberg cell. Hodgkin's granuloma. Imprint. (EA-65. × 2600)

Fig. 23. Multinucleated Reed-Sternberg cell. Hodgkin's granuloma. Section. (H. & E. × 2600)

Fig. 24. Cells from metastatic breast carcinoma. Imprint. (Wright-Giemsa. × 2600)

Fig. 25. Cells from metastatic breast carcinoma. Imprint. (EA-65. × 2600)

Fig. 26. Cells from metastatic breast carcinoma. Section. (H. & E. × 2600)

Fig. 27. Small cells from anaplastic oat cell carcinoma. Imprint. (Wright-Giemsa. × 2600)

Fig. 28. Small cells from anaplastic oat cell carcinoma. Imprint. (EA-65. × 2600)

Fig. 29. Small cells from anaplastic oat cell carcinoma. Section. (H. & E. × 2600)

Fig. 30. Cells from metastatic adenocarcinoma, axillary lymph node. Imprint. (Wright-Giemsa. × 2600)

Fig. 31. Cells from metastatic adenocarcinoma, epitrochlear lymph node.* Imprint. (EA-65. × 2600)

Fig. 32. Cells from metastatic adenocarcinoma, axillary lymph node. Section. (H. & E. × 2600)

Fig. 33. Cells from alveolar cell carcinoma of lung. Imprint. (Wright-Giemsa. × 2600)

Fig. 34. Cells from alveolar cell carcinoma of lung. Imprint. (EA-65. × 2600)

Fig. 35. Cells from alveolar cell carcinoma of lung. Section. (H. & E. × 2600)

In this case, extrinsic cells were seen in imprints made by the Wright-Giemsa and EA-65 methods and in tissue sections made from an axillary lymph node. Extrinsic cells were not seen in Wright-Giemsa imprints and sections of epitrochlear lymph node, but several carcinoma cells were found in EA-65 imprints.

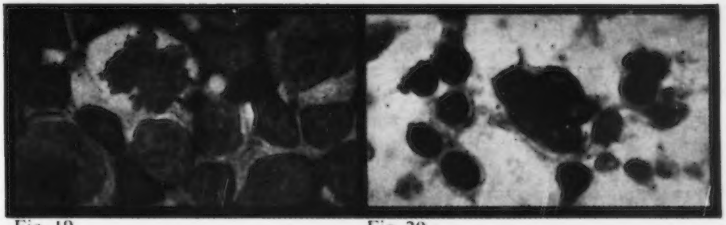

Fig. 19. Fig. 20.

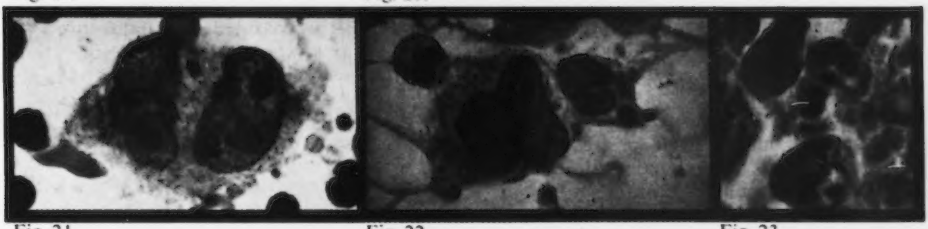

Fig. 21. Fig. 22. Fig. 23.

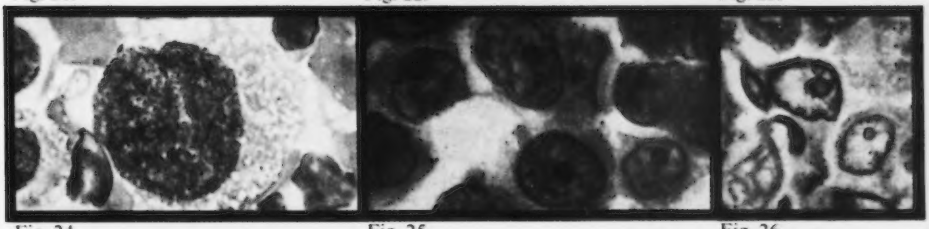

Fig. 24. Fig. 25. Fig. 26.

Fig. 27. Fig. 28. Fig. 29.

Fig. 30. Fig. 31. Fig. 32.

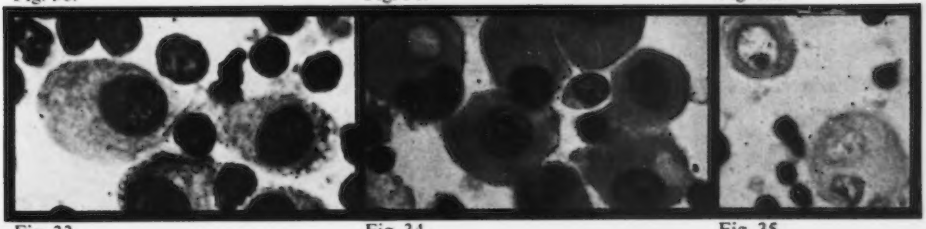

Fig. 33. Fig. 34. Fig. 35.

Wright-Giemsa Stain	EA-65 Stain

Lymphoblasts
(Figs. 13, 14, 15)

Lymphoblasts are the size of large lymphocytes. The nucleocytoplasmic ratio favors the nucleus which is round or irregular and has stippled chromatin. There are usually one to three nucleoli. The cytoplasm stains deep blue and appears granular, except for a clear zone in the areas of nuclear indentation. The cell has a distinct membrane.

Lymphoblasts are not easily identified and are often confused with immature reticulum cells which also have irregular, hyperchromatic nuclei. The irregularity of the nuclear outline, however, appears less striking than in malignant reticulum cells.

Malignant Reticulum Cells
(Figs. 16, 17, 18)

These cells differ from normal reticulum cells by having very large nuclei with clumped chromatin, a distinct nuclear membrane and one to four irregular, blue nucleoli. The cytoplasm is granular, forms a narrow rim around the nucleus and stains blue.

Malignant reticulum cells have a strikingly irregular, hyperchromatic, large nucleus with many coarse chromatin clumps and prominent nucleoli. The nucleocytoplasmic ratio is increased as compared to normal reticulum cells.

Reed-Sternberg Cells
(Figs. 21, 22, 23)

These cells vary in size and are bi- and multinucleated. The nuclei are large and irregular and have a distinct membrane. The chromatin is granular and the nucleoli are huge. The blue-staining cytoplasm darkens along distinct borders. Mitoses are frequent.

The strikingly hyperchromatic nuclei of the single- and multinucleated Reed-Sternberg cells are oval or irregular in shape. They have coarse chromatin clumps and huge nucleoli. The cytoplasm stains uniformly, usually pink, and often has indistinct borders.

Extrinsic Cells
(Figs. 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35)

These elements will vary in appearance according to their origin. In general, the characteristics of carcinoma cells in imprints stained with EA-65 do not differ from those found in other types of cytologic material.

A familiarity with the different cells encountered in imprints permits experienced cytologists and hematologists to use successfully their respective methods as a supplement to tissue studies. The hematologic method may possibly contribute more in the differentiation of cell types in lymphomas, but identification of extrinsic cells is probably easier with Papanicolaou's polychrome stain. Cytologic findings in imprints of lymph nodes in several representative pathologic conditions are very briefly summarized below.

CHRONIC LYMPHADENITIS—Imprints reveal a variability in lymphoid cells, small lymphocytes usually being the most numerous. There are also many macrophages and a fair number of polymorphonuclear leukocytes, histiocytes, plasma cells and mast cells.

LYMPHOID HYPERPLASIA—Imprints have a predominance of lymphocytes at various stages of maturity.

LYMPHOCYTIC LYMPHOSARCOMA AND CHRONIC LYMPHATIC LEUKEMIA—Imprints contain almost exclusively small lymphocytes of uniform size.

LYMPHOBLASTIC LYMPHOSARCOMA—Imprints reveal a large number (20% to 40%) of lymphoblasts.

RETICULUM CELL SARCOMA—Imprints show a uniform hyperplasia of large, malignant reticulum cells.

GIANT FOLLICULAR LYMPHOMA—Imprints display a variability in cell types, with predominance of immature lymphocytes, occasional lymphoblasts, and numerous mitotic figures. It is very difficult to make the diagnosis from imprints.

HODGKIN'S DISEASE—Imprints have a uniform cell type in Hodgkin's sarcoma. In classical Hodgkin's granuloma, imprints reveal Reed-Sternberg cells, lymphocytes and eosinophils.

METASTATIC TUMORS—Imprints show extrinsic cells which are usually noted by their large size, characteristic outline and staining reaction, large nuclei and often prominent nucleoli. They are frequently arranged in clusters. Vacuolation of the cytoplasm is frequent, especially in adenocarcinoma. The cells of oat cell carcinoma, however, may appear indistinguishable from lymphocytes.

Using lymph node imprints, one can successfully support and supplement tissue diagnoses by detailed analysis of the cellular types represented. Occasionally one may find extrinsic cells which, if present in small number, may be overlooked otherwise. The practicing physician who performs lymph node biopsies will be providing a good service to his patients if he supplements the routine tissue studies with touch preparations made from freshly excised lymph nodes. The procedure for making satisfactory touch preparations, although technically slightly different from that for gynecologic smears, is equally simple. In view of the increasing use of cytologic methods for the detection of malignant neoplasms of the uterus, lung and other organs, it is appropriate to recommend this practical and valuable procedure to physicians.

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Dr. Milton T. Edgerton (Johns Hopkins University, Baltimore) warned that evidence continues to show that even light doses of irradiation to the neck region of children may cause the development of thyroid carcinoma. He reported that in one study over 70% of 47 patients with thyroid cancer -- all under 17 years of age -- had a previous history of X-ray therapy to the head, neck or upper chest. The period of time between exposure to X ray and the diagnosis of thyroid malignancy ranged from three to 14 years. These findings are consistent with those found in other larger series compiled by a number of investigators in recent years. In another survey of 180 children with thyroid cancer, 80% had had exposure to X ray of the face, neck or adjacent areas.

The conditions for which children commonly receive X-ray therapy include enlargement of the thymus, acne vulgaris of the face or neck, hemangioma of the face or neck, laryngeal polyps, tonsillitis, enlargement of cervical lymph nodes, pharyngitis, sinusitis and hypertrichosis of the neck. Closer study may reveal even greater incidence of thyroid tumors following exposure to X ray. It is felt that considerable responsibility is placed on any physician who uses irradiation for benign disease.

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Dr. Richard H. Overholt (Tufts University School of Medicine, Boston) summarized his experiences with 635 patients who were operated for lung cancer since 1932. Included in this survey were 100 consecutive cases in which exploratory surgery was undertaken because of unidentified, abnormal radiologic density. In this questionable group of patients, bronchogenic cancer was found in 40%. Dr. Overholt stated that the risk of cancer in such cases far outweighs the risk of surgical exploration, particularly in view of an operative mortality of only 2% in his recent series.

The five-year survival rate of patients treated for these early lesions far exceeds that of the total group of patients with bronchogenic carcinoma. Of the patients who underwent surgery before any apparent spread of the disease, 50% survived five years or more; in patients with hilar or

mediastinal lymphatic involvement, the five-year survival rate was about 20%; in patients with extensive disease, it was only 7%.

Dr. Overholt declared that it is now his policy to resect the cancer-bearing lung and principal tumor mass unless massive mediastinal invasion has created insurmountable problems in hilar resection, vessel ligation or bronchial closure. In addition to removal of the primary tumor mass, such surgery accomplishes several important objectives: the involved bronchial system is protected from possible flooding by blood and secretions; there is immediate cessation of absorption of the products of secondary infection which frequently develops distally to the bronchial obstruction; tumor embolization from the cancer mass is prevented.

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Dr. J. W. J. Carpender (University of Chicago), discussing the use of radiation therapy for early vocal cord cancer, reported that radiation achieved five-year survivals in 18 of 26 patients whose glottic lesions were still limited to Stages I and II. When radiotherapy alone was used for more advanced lesions, there were no five-year survivals. He stated that although favorable results have been achieved with laryngofissure in early lesions, the results with radiation appear to be as good and there is better preservation of the voice.

In the case of lesions of the subglottis and supraglottic area (except very early lesions), surgery remains the treatment of choice. Such surgery should be radical and should include bilateral neck dissection because of the high incidence of metastases in such cases. In very early lesions, supervoltage therapy can be attempted first; if this fails, subsequent radical surgery can be done.

Errata

CA-Bulletin of Cancer Progress, Volume 10, number 5, page 178, September-October, 1960: In the abstract of the paper by W. O. Umiker, column 2, line 12, the figure "28" per cent should read "38" per cent. In the same column, the sentence beginning on line 17 should read: "It provided the only microscopic evidence of malignancy before operation or necropsy in only two instances."

COMING MEDICAL MEETINGS

Date	Meeting	City
1960		
Nov. 4-5	Association of Clinical Scientists	Washington
Nov. 4-5	Central Society for Clinical Research	Chicago
Nov. 15-19	Puerto Rico Medical Association	Santurce
Nov. 17-20	Southern Thoracic Surgical Association	Nassau
Nov. 18-19	American Medical Writers' Asssociation	Chicago
Nov. 26-28	American College of Chest Physicians	Washington
Dec. 1-3	Western Surgical Association	Detroit
Dec. 4-9	Radiological Society of North America	Cincinnati
Dec. 6-8	Southern Surgical Association	Boca Raton, Fla.
Dec. 10-28	Lahey Clinic Fellowship Lectures	Boston
1961		
Jan. 7	Northwest Society for Clinical Research	Vancouver, B. C.
Jan. 8-13	American Academy of Orthopaedic Surgeons	Bal Harbour
Jan. 26-28	Western Society for Clinical Research	Carmel-by-the-Sea, Calif.
Jan. 30-Feb. 3	Clinical Congress of Abdominal Surgeons	Miami Beach
Feb. 6-7	American Academy of Pediatrics	Boston
Feb. 8-10	American Academy of Occupational Medicine	Detroit

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